Public Health England

Public Health England

National Mycobacterium Reference Laboratory &

Regional Centre for Mycobacteriology

for South and Southeast England

User Manual September 2015

The NMRL is a constituent laboratory of PHE National Infection Services

The NMRL is a WHO Supranational Reference Laboratory

The NMRL is a lead partner of the European TB Reference Laboratory Network

The NMRL is part of the Clinical TB and HIV Group, Blizard Institute,

Barts and the London School of Medicine, Queen Mary College

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National Mycobacterium Reference Laboratory (NMRL)

The National Mycobacterium Reference Laboratory (NMRL) is an accredited constituent reference laboratory of the National Infection Service (NIS) of Public Health England (PHE). The NMRL is PHE's National Reference Centre and the Regional (South and Southeast England) Centre for Tuberculosis.

The principal activities of the NMRL include: primary isolation service including microscopy and culture; Fastrack (PCR) Service for detection of *M. tuberculosis* complex and rifampicin (and multidrug) resistance; molecular based rapid identification of *Mycobacterium* sp isolates; drug susceptibility testing for first line and reserve drugs; and molecular epidemiological typing and support of outbreak investigations/contact tracing. Interferon Gamma Release Assays for detection of latent infection and diagnosis are also carried out.

The NMRL initiated the first national molecular detection and drug resistance service for patient specimens and with centres in Germany, Estonia and Russia developed and initiated new rapid liquid culture analyses for reserve drugs susceptibility testing (DST).

The NMRL provides comprehensive molecular epidemiological typing and analyses of outbreaks. Our activities support surveillance activity for TB in the UK.

The NMRL is based in the Blizard Institute of Barts and the London School of Medicine, Queen Mary College where it forms part of the Clinical TB and HIV Group.

The Group's research interests relate to all aspects of tuberculosis and other mycobacterial diseases, respiratory infections, and HIV particularly its interaction with TB; we focus on disease diagnosis, the molecular epidemiology of TB and HIV, understanding drug resistance and disease tropisms, and broader public health problems posed by these diseases both in the UK and overseas.

We have staff working on collaborative national and international clinical, laboratory and public health topics relating to TB.

The NMRL is a WHO Supranational Reference Laboratory for *M. tuberculosis* DST; together with centres in Germany, Sweden and Belgium, it co-ordinates EQA for DST across the EU and non-EU states in the WHO Euro region. It is also a member of the WHO Global Laboratory Initiative involved with the development of WHO/IUATLD strategies for management of mycobacterial diseases and participates in international EQA schemes receiving samples and dispatching to designated regions. The NMRL, with the ECDC, co-ordinates the European Reference Laboratory Network for mycobacterial disease.

NMRL contact details

Public opening hours 9 am to 5:15 pm Monday to Friday

Main numbers: Telephone 020 7377 5895; Fax 020 7539 3459

Enquiries	**NMRL@phe.gov.uk**	**020 7377 5895** **0208 882 2572**
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Safety Officer	**Mrs Melanie Kemp** **Melanie.Kemp@phe.gov.uk**	**020 7377 5895** **020 7882 2575**

General results enquiries are addressed by our administrative staff initially who will direct clinical and technical enquiries to the appropriate staff. There is daily cover for clinical and technical issues and asking for a specific named individual may not be the fastest option (e.g. they are on annual leave). Complex cases are discussed further internally and the advice returned will often be a product of this discussion not just the opinion of the person answering the call. We record the advice given for continuity. We must know the identity both of the patient and the caller.

Summary of Services

- **Please note that although analyses will generally be provided free to the NHS, where a patient specimen is sent a charge will be incurred. Non-NHS specimens will be charged.**
- **Identification of *Mycobacterium sp* isolates** (this is provided free to the NHS and is a rapid molecular DNA-amplification based identification service)
- **Drug Susceptibility Testing for *M. tuberculosis* complex** (phenotypic culture based for first-line drugs on solid media and rapid liquid culture based for reserve drugs; this is provided free to the NHS)
- **Drug Susceptibility Testing for Non-Tuberculous Mycobacteria (NTM) (**phenotypic culture based testing for clinically significant NTM isolates; this is free of charge for patients under 18 years old)
- **Molecular Epidemiological Service** (e.g. outbreak investigations, laboratory cross-contamination, provided free to the NHS)
- **Interferon Gamma Release Assay** (latent TB infection diagnosis)
- **Primary Isolation Service** (including microscopy and culture)
- **Fastrack (PCR) Service** (molecular detection of *M. tuberculosis* complex and rifampicin resistance or multi drug resistance in primary specimens and cultures respectively)
- **Clinical and Technical Advice**
- **Clinical Advice for case and outbreak investigation and management**
- **Computerised database on laboratory confirmed cases**
- **Archived collection** of *Mycobacterium* isolates for epidemiological analysis
- **Training**
- **Research and Development**

For further information concerning services or matters of interest visit the PHE web-site at https://www.gov.uk/government/organisations/public-health-england

Services Available

For further information and advice on these services please call 020 7377 5895.

Samples/cultures <u>cannot</u> be received after 17:15.

Please note all turnaround times are dependent upon the receipt of a pure culture containing sufficient bacteria for analysis. At least 90% of all samples will be available at the Turnaround times listed below.

We endeavour to assist laboratories by treating contaminated cultures to purify mycobacteria rather than returning them to the sender.

Reference Service

Identification of cultures of AFB	**Rapid identification of *M. tuberculosis* complex and some common Non-Tuberculous Mycobacteria (NTM) using molecular techniques.**	**For cultures received before 9:30 am within 1 working day. All other cultures are processed the following day.** **A report sent out within 2 working days of culture receipt**
	DNA sequencing and phenotypic tests are performed when identification is not possible by the above method.	
M. tuberculosis		
First Line Sensitivities	**Isoniazid, rifampicin, ethambutol, pyrazinamide.**	**A report sent out within 2-3 weeks of culture receipt**
Reserve Drugs	**Ofloxacin, moxifloxocin** **Amikacin, kanamycin, prothionamide, capreomycin**	**A report sent out within 2-3 weeks of request for these sensitivities, Identification of rifampicin resistance or MDRTB in referred cultures.** **The NMRL pro-actively analyses cultures produced at NMRL from patient specimens submitted to our national Fastrack Molecular diagnostic service. If rifampicin resistance mutations are detected (predictive of MDRTB) we will automatically analyse cultures for first-line and reserve drugs.**
Additional Reserve Drugs	**Linezolid** **PAS** *(this is performed rarely and the exact correlation with clinical efficacy is unclear)***Streptomycin** *(only tested on request)*	**A report sent out within 2-3 weeks of request for these sensitivities or identification of XDRTB**
Non-tuberculous Mycobacteria*		
	Rapid growers: Cotramoxazole, Linezolid, Ciprofloxacin, Moxifloxacin, Cefoxitin, Amikacin, Doxycycline, Clarithromycin and Tobramycin, Imipenem	**A report sent out within 1-2 weeks of culture receipt**
	Slow growers: Clarithromycin, Ethambutol, Rifampicin	**A report sent out within 2-3 weeks of culture receipt**

Please note the antibiotic panel tested for NTM will vary depending on the organism identified.

Primary Service

Microscopy performed within 1 working day of sample receipt.	**Microscopy report sent out within 1 working day.**
Decontamination and culture of clinical samples on liquid and solid media.	**Final Negative result reported after 6 weeks (or 8 weeks for blood cultures and CSF samples)**
Culture of blood and bone marrow	**NB. Incubation will be continued for up to 12 weeks, but a further report is not issued unless culture becomes positive**
Incubation of inoculated blood and bone marrow cultures	

Molecular Epidemiology Service

VNTR- MIRU analysis	**Final report within 4 weeks of receipt of a suitable culture.**
Confirmation of rapid fingerprinting by further VNTR-MIRU analysis (or other appropriate methodology)	**Report telephoned (or final written report) within 6 weeks of receipt of a suitable culture.**

Fastrack Service

Rapid PCR service for the detection of *M. tuberculosis* complex and Rifampicin/Isoniazid resistance.	**Appropriate cultures received by 9:30 am, analysed daily and results communicated to sending laboratory within 1 working day.**
Rapid PCR service for *M. tuberculosis* complex and Rifampicin resistance detection in pulmonary & CSF samples	**Appropriate pulmonary & CSF samples received by 9:30 am, analysed daily and results communicated to sending laboratory within 1 working day.** **NB.** *Minimum CSF volumes are required* ***(0.5 ml).*** *We will also culture residual material for maximum sensitivity*
Rapid PCR service for *M. tuberculosis* complex and rifampicin resistance detection in non-pulmonary samples (except CSFs)	**Samples received before 9:30 am Wednesday, results communicated to sending laboratory by Friday.** **NB.** *For paraffin wax blocks, the* ***whole wax block*** *must be sent along* ***with a diagram/slide*** *indicating the area where AFB /granuloma were seen*

The NMRL pro-actively analyses cultures produced at NMRL from patient specimens submitted to our national Fastrack Molecular diagnostic service. If we have detected rifampicin resistance mutations (predictive of MDRTB) we will automatically analyse cultures for first-line and reserve drugs at no further cost to the NHS. This is a major contribution to our public health role.

Interferon Gamma Release Assay

Quantiferon Assay	**Reports sent out within 10 working days of receipt of sample.**

Clinical and Technical Advice

Incoming calls for clinical and technical advice available Monday-Friday 9:00 to 17:00.

Key factors affecting specimen performance

If a specimen is received at the NMRL, which is unsuitable for examination, we will endeavour to contact the sender to discuss the problem.
If a specimen is submitted to NMRL for an investigation that we do not offer we will temporarily archive the sample/isolate and issue a report to the sender explaining the reasons for the sample's rejection.

Reference service

The time taken to perform bacterial identification and drug susceptibility tests is dependent on the receipt of pure viable cultures. Cultures that require purification or that cannot be retrieved because they are no longer viable and necessitate a second isolate may increase turnaround time significantly. Our approach is to assist you wherever possible by not rejecting contaminated cultures; however submitting a second culture is usually the best strategy.

If an aliquot of a liquid culture is to be sent then a concentrated sample is best. Transfer **1 ml** of the concentrated sample to a sterile universal or cryovial/microcentrifuge tube for transport, and store the rest of the sample (1-2 ml) at your laboratory.

Leaking culture samples will <u>not</u> be processed and a report will be issued informing the user of this.

Primary Service

- The specimens to be sent should be as fresh as possible.
- Nothing should be added to the sample except when the specimen is a small piece of tissue in which case sterile saline or sterile water should be added. ***Do NOT use formalin as this will kill the mycobacteria***.
- Blood samples and Bone Marrow samples (minimum volume of 2 ml) for culture should be sent in a vacutainer containing lithium-heparin. ***(Mycobacterial survival is lower in EDTA tubes).***
- We strongly recommend that specimens are refrigerated if any delays in submission to the NMRL are likely.
- We do not usually perform microscopy on urine specimens; we only culture early morning urine specimens.
- **If you wish to send samples of non-human origin please contact the NMRL clinical staff <u>*before*</u> sending.**

Fastrack Service

This is our rapid national molecular diagnostic service for primary samples and positive cultures to detect MTBC and rifampicin resistance (and isoniazid resistance in cultures only).

Ideal specimens are smear positive primary specimens or a positive culture. Other specimens have lower sensitivities for detection (see Sam et al Emerging Infectious Diseases (2006) 12: 752-9; Seudi et al *Thorax* (2012) 67:361–367)

Generally smear positive samples are more likely to be successfully analysed as they have a higher Acid Fast Bacilli (AFB) load. As part of Fastrack, the NMRL pro-actively analyses specimens shown to be rifampicin resistance for isoniazid resistance and any resulting cultures from specimens containing MTBC with rifampicin/isoniazid resistant mutations (predictive of MDRTB) are pro-actively analysed for first line and reserve drugs at no further cost to the NHS. We see this as a major contribution to our public health role for clinical management and limitation of the further development and spread of drug resistant TB

In general, dilutional fluid samples (e.g. CSF, pleural fluid, ascites etc) have much lower sensitivities; the minimum amount of CSF that will be examined is **0.5ml *(not supernatant)***. However submitting the largest possible volume of CSF and other fluids will increase the sensitivity. Please submit as much of these fluids as possible-you can never submit too much!

Lysed blood or heavily bloodstained samples can interfere with PCR based reactions. DNA in specimens requesting molecular tests may degrade if stored for too long before referral.

Paraffin wax blocks can be examined but sensitivity is lower than that for fresh tissue. In these cases the whole wax block must be sent along with a diagram/slide indicating the area where AFB /granuloma were seen to aid sampling. This will be returned to the sender on completion of the Fastrack analysis.

Interferon Gamma release Assay

Blood should be collected in the tubes provided (follow instructions) and incubated within 16 hours of collection at 37^{o}C for 16-24 hours, before sending. Samples must reach NMRL within 72 hours of removal from incubation. ***If sent before incubation please clearly indicate as such on the form***.

Contact tracing/case meeting

We are frequently asked to attend case meetings (or via teleconference) for complex patients and larger contact tracing investigations in institutions such as schools, prisons and health care institutions. We will try and assist where possible, but requests with less than 1-2 working days' notice of the meeting are unlikely to be feasible.

Referral of specimens/cultures

No specimens or cultures are referred to other laboratories. If other investigations are required at another laboratory then it is strongly recommended that a further specimen/culture is sent by the sending laboratory directly.

NMRL Price List
April 2015-March 2016

METHODS	REQUEST	NHS/PHE PRICE * (per isolate/sample)	NI/SC/CI PRICE** (per isolate/sample)	NON-NHS PRICE ** (per isolate/sample)
Identification of submitted cultures and first line drug testing on solid media (no charge if within the remit of the PHE).	**ID and Sensitivity**	**£0**	**£66.24**	**£88.32**
Reserve drugs for DST	**Extra Sensitivities**	**£0**	**£49.68**	**£66.24**
Molecular epidemiology of TB cultures * **	**Molecular Epidemiology**	**£0**	**£41.95**	**£55.20**
Non-Tuberculous Mycobacteria (NTM) DST	**ID and Sensitivity**	**£58.00**	**£58.00**	**£75.00**
Primary specimen receipt and inoculation into standard solid and liquid culture medium.	**Culture**	**£36.43**	**£36.43**	**£49.68**
Blood/bone marrow Standard liquid. culture	**Culture**	**£36.43**	**£36.43**	**£49.68**
Fastrack: PCR identification of *M. tuberculosis* complex and molecular rifampicin testing (includes culture of residential material and identification of resulting cultures).	**Fastrack**	**£137.16**	**£137.16**	**£198.12**
Quantiferon Gold for diagnosis of latent infection and active tuberculosis (based on purchase of 10 tests at a time	**IGRA**	**£45.72**	**£45.72**	**£45.72**

NOTE: Where samples are unsuitable for testing (leaking, incorrect container, unlabelled specimen,) or are submitted with no or incomplete request forms, a fixed administrative charge of £14.35 will be applied.

* = Internal Recharging (NHS/PHE) ** = External Recharging

***=Outside of outbreak investigations we do not analyse non NHS/PHE cultures without prior agreement

Please note all above prices are subject to VAT

SPECIMEN AND SAMPLE SUBMISSION GUIDELINES

All Specimens MUST be labelled with the following:-

1) Surname/Forename, or other Unique Patient Identifier
2) Sender's Sample Number
3) Date of Birth

Request Forms MUST match and include the above information on the sample the list below
And the Name and contact information of requester (telephone number vital for urgent requests)

4) Tests required
5) Sample type
6) Specimen/Isolation site
7) Date of dispatch
8) NHS Number
9) Sex
10) Date and time of collection of specimen
11) Relevant clinical information

Request Forms to accompany specimens/cultures

- Please ensure the appropriate NMRL request from is fully completed for the sample being submitted with the required information as stated above (1-11) as well as the correct telephone number, particularly for Fastrack requests.
- Each sample must be accompanied by an individual request from, even if more than one sample is submitted from the same patient.
- Please complete the forms in **BLACK** or **BLUE** pens (**NOT** RED or any other colour).
- The space marked **"For NMRL Use only"** is intended for use by NMRL staff. Please do not write in this space.
- The PHE NMRL laboratory advises users where forms are poorly completed. Wherever possible the NMRL supports its users by not rejecting referred specimens and cultures.
- There are four NMRL request forms, these are as follows:
    - **Mycobacterium Referral Form (primary samples and positive cultures) (N1)**
    - **Fastrack Request Form (N2)**
    - **Molecular Epidemiology Request Form (N3)**
    - **QuantiFERON®-TB Gold test (N4)**
- NMRL request forms can be downloaded from the following website: https://www.gov.uk/government/collections/national-mycobacterium-reference-laboratory-nmrl, or ordered pre-labelled with the requestor code and address from the PHE LIMS department via e-mail (Limshelpdesk@phe.gov.uk).

GUIDANCE ON PACKAGING SAMPLES

The PHE has a short film clip to provide guidance for referring laboratories on how to package samples to the required standard.
http://webarchive.nationalarchives.gov.uk/20140722091854/http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/MicrobiologicalTestsAndServices/cfi40Packagingguidance/

A small but significant proportion of samples received by the PHE Reference Microbiology Services are poorly or inappropriately packaged. This often leads to samples leaking or being damaged during transport, therefore posing a serious risk to PHE staff handling them. PHE hopes to eliminate this risk by helping laboratories to understand basic packaging requirements.

The following guidelines are intended to cover the transport of clinical samples from humans, or cultures of micro-organisms isolated from such samples to another laboratory for diagnostic or other clinical testing within the U.K. where the micro-organisms suspected of causing the disease are all either Hazard groups 2, 3 or 4.

The terms Category A and Category B are limited to classifying samples / microbial cultures being transported to another laboratory.

Sample Description	**Packaging Requirement**
Category A samples are known or suspected to contain a microbial agent with the following definition *"an infectious substance which is transported in a form that if exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease to humans or animals"* (see indicative list) The majority are Hazard Group 3 or 4	Assign to UN2814 (Humans) Packaging Instructions PI620 Supporting documentation as per ADR Transport as category A ADR licensed courier
For practical reasons to allow referral / reference services to continue a limited number of Category A agents have exempted from being transported as Category A. These are Vero-cytotoxin producing Escherichia coli (VTEC), Mycobacterium tuberculosis and Shigella dysenteriae 1	Assign UN3373 Packaging instruction PI650 Send by courier Royal mail will **NOT** accept
Category B samples are those that do not meet the definitions of Category A	Assign UN3373 Packaging instruction P1650 Post or courier Royal mail WILL accept

These guidelines are not intended as a substitute for reading the advice given by DfT and DoH.
Use the links below for further information.

https://www.gov.uk/shipping-dangerous-goods/overview
https://www.gov.uk/government/organisations/department-for-transport/series/transporting-dangerous-goods
http://www.who.int/ihr/publications/who_hse_ihr_2012.12/en/
http://www.icao.int
http://www.unece.org

Reporting incidents during transportation that may affect the safety of personnel:

The NMRL will report to users any leaking containers and improperly packaged parcels.
Leaking cultures will not be processed by the NMRL, users will be informed and a repeat sample requested.
Repeated offences will be referred to the PHE Safety Committee who may refer to the Health and Safety Executive.

Labelling and Packaging (NMRL)

All specimens/cultures sent to the NMRL must be packed in accordance with IATA regulations 650/602.

Label the specimen/culture bottle with the name of the patient (or unique identifier) and the laboratory number.

The top of the specimen/culture bottle must be fixed on firmly so that there is no chance of leakage. It may be necessary to use parafilm to ensure that the top remains on tight during transport. This will also prevent desiccation of the specimen/culture in transit which will compromise successful culture. Wrap the bottle in absorbent material and seal inside a minigrip bag.

The NMRL will endeavour to process ***primary*** material if leakage occurs but this is likely to compromise the chance of successful culture, and we will request the user to send us an additional specimen.

Leaking ***cultures*** will ***NOT*** be processed and a repeat sample will be requested.

Place the specimen/culture inside a leak proof plastic container with enough absorbent material to be able to absorb all the contents of the bottle in case of leakage.
Place the plastic container inside a fibreboard box.
Place the form between the plastic container and the outer cardboard box. DO **NOT** PLACE IT INSIDE THE PLASTIC CONTAINER. In the event of leakage/breakage the whole shipment will be destroyed without opening.

Specimens may be sent by Royal Mail or Courier.

We recommend that to minimise delays specimens, especially those sent for our Fastrack molecular diagnostic service, are sent by routine courier e.g. DX or other specialised courier.

Please ensure that the courier is able to reach the NMRL before 1700h.

Cultures can only be sent by courier.

Faxing and emailing reports containing patients' data.

It is our policy that reports containing patient data should not be sent by routine E-mail. E-mails cannot be relied on to guarantee security of patient data because they can be intercepted by a third party on route (unless encrypted).

In some circumstances NMRL can send results by fax. In this case the following conditions must be adhered to (refer also to the document "PHE recognition of Caldicott recommendations"):

- The report must be sent to a "safe haven" fax machine. This means that, if the location is in general use, consideration must be given to ensuring that unauthorised personnel are unable to read reports, accidentally or otherwise. Also, the room housing the fax machine must be in a secure location, which is locked if it is likely to be unattended at the time the fax is sent.

- Assurance must be sought from the intended recipient of the faxed report, in writing, that the receiving fax machine is a safe-haven. If it is essential to fax patient identifiable information to NMRL please speak to the administration office at NMRL who will arrange for someone to receive the fax. Our fax machine is a "safe haven" fax machine

- It is a requirement that any recipient of a fax from the NMRL confirms that the fax has been received. No faxes will be sent to centres refusing to confirm the safe receipt of faxes.

Compliance with the Human Tissue Act
Submitting tissue samples from deceased people

The PHE Microbiology Services is licensed by the Human Tissue Authority (HTA) (Licence number 12459) to store tissues from deceased people for scheduled purposes. Post mortem samples are submitted to PHE Microbiology Services by coroners or pathologists for examination to help them determine the cause of death.
As part of our public health remit, we sometimes need to retain these samples for the purpose of public health monitoring which is defined as a scheduled purpose within the Human Tissue Act 2004. Further analysis of these samples may help determine the cause of an outbreak due to an infectious disease or may allow identification of new strains of infectious agents at a later date.

Obtaining consent to remove, store and use human tissues for a scheduled purpose is one of the underlying principles of the Human Tissue Act. PHE Microbiology Services receives post-mortem samples from Coroners' post-mortems or from NHS establishments across the UK and therefore we are not in a position to either seek consent ourselves or have arrangements in place to confirm that the requirements of the Act have been complied with by the sender.

We would ask coroners and pathologists who send post mortem samples to PHE Microbiology Services to provide us with details of consent, and would also ask that consent includes retention of the samples for the purpose of public health monitoring.

When tissue samples from deceased people are received at the PHE Microbiology Services they are retained securely and confidentiality is maintained in compliance with Caldicott principles as are all samples received at this centre. It is normal practice for tissue samples from the deceased to be disposed of in the same way that all others clinical samples we receive are disposed of. However, we will adhere to any specific requirements regarding disposal or returning tissue samples if requested by the sending coroner or pathologist.

PHE Microbiology Services recognition of Caldicott recommendations

The recommendations of the Caldicott report (1997) have been adopted by the Public Health England (PHE). These recommendations relate to the security of patient identifying data (PID) and the uses to which they are put.

The PHE observes Caldicott guidance in handling PID and has an overall Caldicott Guardian who is the Director of Health Protection and Medical Director who reports through the Information Governance and Caldicott functions and onwards to the National Executive.

The PHE Microbiology Services has a Caldicott guardian who advises the Director of Microbiology Services on confidential issues and is responsible for monitoring the physical security of PID in all parts. This also applies to the transfer of results of investigations to and from PHE Microbiology Services whether by mail services; telephone or fax. The value of 'safe haven' arrangements or other means of the sender and receiver information identifying themselves to each other before data is transferred is emphasised.

The PHE is anxious to audit the security of its PID in collaboration with its customers. Customers are invited to review our arrangements in conjunction with individual laboratory directors and/or the Caldicott Guardian. Customers are also asked to draw to the Caldicott Guardian's attention any instances where PID security has been threatened or has broken down.

Any uses that PID are put to outside the clinical diagnostic services generally allow patient identifiers to have been removed before hand, and when PID is used for research purposes the proposals are considered first by the appropriate Ethics Committee. All enquiries regarding the security and use of PID should be addressed to the Caldicott Guardian at: NMRL@phe.gov.uk

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